are the susceptible type. Even though the improvement is temporary, it is of great value because it shortens the period of "cooling down," necessary before diagnostic procedures to determine, and surgical procedures to cure the underlying cause, can be carried out.

It has been of particular value in many cases of chronic pyelonephritis. These cases were often completely resistant to pelvic lavage, and even to Mandelic acid, because there are foci of infection in the kidney parenchyma itself. Sulfanilamide was able to clear these deep foci because of its humoral action.

The response of pyelonephritis in pregnancy has been superior to that induced by Mandelic acid or hexamin, and it is much more easily tolerated than the former. It has no demonstrable effect on the infant. The only failures have been in those patients having a high degree of hydronephrosis. The placement of indwelling catheters in these, and reinstitution of sulfanilamide therapy have successfully carried several patients over periods when they were too ill to even allow therapeutic abortion.

The treatment of two other genito-urinary infections should be mentioned. Sulfanilamide is almost specific for lymphogranuloma inguinale. If given early the inguinal bubo practically always subsides without suppuration, and even after suppuration has occurred the sinus rarely persists. The control of chancroidal infection has likewise been made less difficult. There have been no cases of extensive phagadenic ulceration with its resultant deformities since the use of sulfanilamide on mixed infections.

IN CONCLUSION

The use of sulfanilamide does not dispense with the need for careful urologic diagnosis, but on the contrary makes it more important, for only with a knowledge of the entire anatomic, physiologic and bacteriologic status can the proper use of the drug be made in producing rapid permanent cures.

In upper and middle urinary tract infections its greatest value probably lies in control of sepsis before and after cystoscopic or surgical procedures.

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GONORRHEA: ITS TREATMENT BY ARTIFICIAL FEVER, AND BY FEVER THERAPY IN COMBINATION WITH SULFANILAMIDE*

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DURING the past few years the treatment of gonorrhea has twice been revolutionized by the introduction of new methods. I refer to the use of artificial fever therapy and to the still more recent advent of the use of sulfanilamide. Either of these agents used alone will produce results that would have been considered unbelievable a decade ago, but it is their combined, synergistic use which today offers the optimum chance of cure in cases found resistant to the use of sulfanilamide and local therapy alone.

AUTHORS' STUDIES

Our fever therapy department was inaugurated in July, 1936. From that time to March 1, 1939, we have given 931 treatments to 279 patients. Of these, 205 patients were treated for definitely proved gonococcic infections. We must eliminate from this group those on whom our follow-up data are insufficient, also those who for various reasons did not complete the treatment as outlined for them. This leaves a total of 160 patients, which will be divided into three groups and discussed in the order named:

(*a*) Single ten-hour fever at 106.7 degrees, 100 patients.

(*b*) Short multiple fever, combined with sulfanilamide, 55 patients.

(*c*) Fever equal to the thermal death time of the patient's own gonococcus, 5 patients.

The beginnings of our fever therapy department were inspired largely by the work of Stafford L. Warren and his colleagues at the University of Rochester Hospital in Rochester, New York. In 1933 Carpenter, Boak, Mucci, and Warren reported the *in vitro* thermal death time of fifteen strains of N. gonorrheae.[1] This was found to vary from seven to twenty hours at 106.7 degrees Fahrenheit.

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In a more recent work[2] the same authors have reported the thermal death time at 106.7 degrees Fahrenheit on 250 strains of the gonococcus. This showed a variance of from six to thirty-four hours, with a mean of sixteen hours. In 75 per cent of the strains the thermal death time was between eleven and twenty-one hours. These laboratory data furnish a convincing rationale for the use of long sustained single fevers for the treatment of gonorrhea. Warren, after having determined the thermal death time of the patient's own strain of gonococcus, gave the patient a single febrile session of equal duration and intensity. By the use of this method he reported a high percentage of cure.[3,4]

OBSERVATIONS

In the early part of our fever work, we lacked the facilities for determining the thermal death time of each patient's gonococcus. We, therefore, arbitrarily selected ten hours at 106.7 degrees as an optimum amount of fever to be given at one session, and used this as our routine treatment from July, 1936, until sulfanilamide came into use for the treatment of gonorrhea.

Fevers of this height and duration are not to be undertaken lightly. Each patient must be carefully studied before fever therapy is attempted. A detailed history is taken. Because of their relation to liver damage, alcoholism and previous attacks of jaundice are carefully noted. The patient is subjected to a searching general physical examination, including a urinalysis and a blood Wassermann test. Smears and cultures must be positive for the gonococcus. The cardiovascular and respiratory systems are further investigated by a competent cardiologist. His studies include an electrocardiogram, fluoroscopy of the heart and chest, measurement of the vital capacity, and an exercise and recovery test.

Several contraindications to the use of long high fever should be mentioned. Patients past forty years of age must be treated with great caution. Patients with electrocardiographic evidence of myocardial damage or heart-block do not tolerate fever well. Mild valvular lesions, if well compensated, do not of necessity contraindicate treatment. Chronic alcoholism and advanced cardiovascular-renal disease contraindicate long-sustained treatment. Patients with acute respiratory infections, especially active pulmonary tuberculosis, should be excluded.

PREPARATION FOR TREATMENT

Two or three days of preparation are advisable before treatment. Preparation should consist of forcing fluids and the giving of a high caloric, high carbohydrate, low fat, and high sodium chlorid diet. Drugs which inhibit perspiration should not be given. The patient should report for treatment without breakfast. The temperature, pulse, respiration and blood pressure are taken and 10 cubic centimeters of blood withdrawn for laboratory studies. The patient is then placed in the prewarmed cabinet. A Leeds and Northrup Micromax strip chart recorder, with a range of 90 to 110 degrees Fahrenheit, is used to record constantly the patient's rectal temperature. The pulse and respiration are charted at fifteen-minute intervals, and the blood pressure is taken every thirty minutes, or oftener if abnormal. A graduate nurse, especially trained for fever therapy, attends each patient constantly during the treatment. One of our medical group is in the office at all times prepared to handle any emergency. Every therapeutic aid for the treatment of emergencies is instantly available, including intravenous solutions in liter flasks, carbogen, and stimulants. We feel that we are thus able to carry out treatments as safely and satisfactorily in our office as in the hospital.

The sedative usually employed, in addition to seconal, grains one and one-half, taken on arrival, is pantopon, grain one-third, given by hypodermic injection when the patient's temperature is 101 to 102 degrees. During long treatments, pantopon, grain one-sixth, or dilaudid, grain one-fortieth, may be repeated once or twice to control restlessness. The patient's temperature usually reaches the desired level in one and a half hours. This point constitutes the starting time of the treatment.

TREATMENT

During treatment the patient is allowed to drink 200 to 400 cubic centimeters of fluid per hour. The fluid most commonly used by us is Calso water, a slightly charged alkaline water containing calcium carbonate, magnesium carbonate, sodium phosphate, sodium chlorid, and sodium bicarbonate in physiologic solution. This water is much more palatable than salt water, and has greatly reduced the incidence of nausea and vomiting. Very rarely is it necessary to resort to the intravenous route to maintain adequate fluid balance.

When the treatment period is over, the cabinet is opened and the patient's temperature allowed to return to normal. This requires from one to one and one-half hours. Following these long treatments, the patient is given an alcohol rub and moved by ambulance to a near-by hospital for observation and rest. The average length of hospital stay in this series was 1.6 days.

ARMAMENTARIUM

We use two fever cabinets of the circulating warm, moist-air type. Our third cabinet uses inductothermy for the elevation of temperature. We have been able to observe no physiologic difference or variation in patient comfort between these so-called external and internal methods of heating. The type of machine used, in our opinion, is of far less importance than the skill of the personnel using that machine. In the selection of a fever machine, such factors as size, convenience, cost, and manufacturer's integrity must, of course, receive consideration. The one most important attribute of a fever machine is its ability to generate and maintain high relative humidity. In a well-designed cabinet, the patient's rectal temperature can be maintained between 106 and 107 degrees with a cabinet temperature not exceeding 110 degrees, provided the humidity is of the order of 90 per cent saturation. Under such conditions dehydration

will rarely occur. The patient's plasma-red cell relationship is determined at frequent intervals by means of the hematocrit, and the fluid intake is adjusted accordingly. We often find it necessary to limit the quantity of ingested fluid to prevent too great an increase in the volume of the plasma. In the rare cases where dehydration does occur, we administer fluids intravenously in the form of 5 per cent dextrose in normal saline.

Another advantage of low cabinet temperature and high humidity is the virtual absence of skin burns. With the older method of low humidity and relatively higher temperature, skin burns and blisters occurred frequently. On several occasions it was necessary to terminate treatment for that reason alone.

COMMENT

At rectal temperatures of 106.7 degrees the pulse rate will average 130 to 140, and the respiration will be 26 to 28. The systolic blood pressure characteristically shows an initial rise during induction of 10 to 20 millimeters. During fever maintenance the systolic pressure will vary between normal and 20 millimeters below normal. Diastolic blood pressure during fever is about one-half the systolic; for some reason not known to us it may be heard down to zero pressure in many cases. A systolic blood pressure below 80, a pulse pressure less than 20, and a pulse rate above 160 lasting for more than a half-hour ordinarily call for termination of the treatment.

During the period from July, 1936, to December, 1937, one hundred patients received a single hyperpyrexia treatment of ten hours' duration at a rectal temperature of 106.7 degrees Fahrenheit. Each patient in this series received at least three subsequent examinations to determine the presence or absence of the gonococcus. In women two of these examinations must be postmenstrual. Since July, 1937, routine cultures have been made on material obtained from these examinations, in addition to the usual smear stained by Gram's method. The majority of these patients were observed for three or more months following fever therapy and many more examinations were made than the minimum stated above. Of these one hundred patients with adequate follow-up, eighty-seven were found to be consistently free of gonococci following the single ten-hour session of fever. Sixty-three patients were classified as acute. There were ten failures in this group (84 per cent cured). Of the thirty-seven patients who had chronic gonorrhea, three failed to be cured (92 per cent cured). The average duration of the acute cases before fever therapy was four weeks and of the chronic cases, 5.4 years. Nineteen of these chronic cases had carried their gonorrhea for from five to twenty-two years before being finally cured with artificial fever. Of these one hundred patients, seventy-seven were male and twenty-three female. It is interesting to note that all of our failures were in male patients.

TREATMENT WITH SULFANILAMIDE

When sulfanilamide began to be used for the treatment of gonorrhea in June, 1937, we discontinued the use of artificial fever. There was a period of several months during which no patient received fever treatment for a gonorrheal condition in our office. It seemed for a time that the use of fever in the treatment of this disease might be relegated to the past. However, as the number of failures from sulfanilamide therapy began to become apparent, we again turned to fever therapy for aid in these sulfanilamide-resisting cases. At this time Ballenger, Elder, and McDonald published a preliminary report on the treatment of gonococcic infection by combined sulfanilamide and thermotherapy.[5]

In combining fever therapy with sulfanilamide chemotherapy, we instruct our patients to take 20 grains of sulfanilamide four times a day for two days preceding fever therapy. On the morning of the fever treatment they are told to take 20 grains of sulfanilamide one hour before reporting for treatment. A fever session of five hours' duration at a rectal temperature of 103.5 degrees is then given. The fever treatment is repeated every other day until three treatments are given. Sulfanilamide, grains 20, four times a day, is administered on the alternate days. In nineteen patients so treated we had five failures, a cure rate of only 74 per cent. At this time we altered the above procedure by increasing the temperature plateau of the three fever treatments from 103.5 to 106 degrees. All other factors remained the same. Up to March 1, 1939, thirty-six patients have been treated by this higher temperature routine with only five failures (86 per cent cured). Taking these two groups as a whole, we have fifty-five patients treated and adequately followed, with ten failures (82 per cent cured). Forty-two cases were acute, with eight failures, and there were two failures among the thirteen chronic cases. The percentage of success in male and female patients was identical, there being eight failures in forty-four males and two failures in eleven females. We wish to emphasize again that, with one exception, this combined treatment has been used only in cases found resistant to sulfanilamide and local therapy.

In each of these cases a blood sulfanilamide level is determined at the beginning of each fever treatment after the method of Proom.[6] A blood level of 10 milligram per cent is considered satisfactory. Experience has shown that the combined treatment is much less effective in patients who do not concentrate the drug to this level.

COMMENT

The advent of sulfanilamide has greatly simplified the treatment of gonorrhea. This drug, combined with mild local treatment, results in cure in 80 per cent of the cases treated. We can cure 86 per cent of the remaining 20 per cent by combined chemotherapy and artificial fever therapy. A combination of these two figures shows that success follows the use of these simple measures in 97 per cent of the cases treated. Fever in these cases does not entail risk. Five-hour fevers, at 106 degrees, may be safely given to patients who could not tolerate ten hours at 106.7 degrees. Patients

receiving five-hour fevers are not fatigued enough to require hospitalization.

THERMAL DEATH-TIME FEVERS

For the unfortunate 3 per cent not cured by sulfanilamide or combined chemo- and thermotherapy, a thermal death-time fever should be considered. Apparatus for determining the *in vitro* thermal death time of the gonococcus was installed in July, 1937. A description of the procedure involved has been published elsewhere.[1,2]

Because of the limited number of cases suitable for such treatment, our series is limited to five patients who have received a fever equal to the thermal death time of their own strain of gonococcus. Four patients—three males and one female—have been given thermal death-time fevers of 12, 13, 14, and 18 hours, with complete cure. These patients were not only sulfanilamide-resistant, but also were not cured by three five-hour fevers at 106 degrees, combined with sulfanilamide.

The fifth patient was a 25-year-old female with a gonorrheal septicemia and endocarditis. She had previously taken large quantities of sulfanilamide without result. A thermal death-time fever of thirteen hours at 106.7 degrees also failed to cure her. The thermal death time was repeated on a blood culture obtained after the fever therapy and again found to be thirteen hours. This apparent failure of a thermal death-time fever may be explained on the basis that this patient's infection was systemic and undoubtedly present in areas, such as the skin of the face and alveoli of the lungs, the temperature of which cannot be maintained at the rectal level.

In every case these long thermal death treatments were very well tolerated. Hospitalization of the first four patients was only for one day or less. These cases, however, require very careful selection. We feel that this arduous procedure should be used only after combined chemotherapy and fever therapy have failed to cure the patient of his infection.

SUMMARY

1. A series of one hundred consecutive patients treated for gonorrhea with a single ten-hour fever session at 106.7 degrees rectal temperature is presented. The incidence of cure was 87 per cent.

2. The use of sulfanilamide provides a simple treatment for gonococcic infections which, when combined with mild local treatment, is 80 per cent effective.

3. A plan is outlined for the use of combined chemotherapy and artificial fever therapy in patients resistant to sulfanilamide and local treatment. This combination has cured 86 per cent of these resistant cases.

4. For the few cases not cured by these combined efforts we would suggest giving a fever equal to the *in vitro* thermal death time of the patient's own strain of gonococcus. This method will result in an incidence of cure approaching 100 per cent.

5. The more simple and less hazardous methods should be tried before resorting to the long fevers ordinarily required in the thermal death-time procedure.

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CLINICAL ASPECT OF ELECTRICALLY PRODUCED GAMMA RAYS*

THREE IMPORTANT UNITS

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THE first large x-ray tube installation in the world for the experimental treatment of cancerous disease was developed by Drs. Robert A. Millikan and C. C. Lauritsen at the California Institute of Technology in Pasadena, and had a 750,000 volt capacity. This was soon replaced by one of two million volts capacity. While this is still the largest tube of its kind, it has now been withdrawn from the clinical field and is used in "atom smashing" physical research. At the present time, in the United States, there are seven or eight public and private institutions operating tubes capable of generating x-rays at a voltage of approximately one million, but these institutions are not yet in a position to evaluate clinical reactions measured in terms of permanent results.

Actually, the largest x-ray tube in the world, of ten million volts potential, will be found at the Carnegie Institute of Terrestrial Magnetism in Washington, D. C. There, work is successfully carried on under the direction of Dr. M. A. Tuve and his associates, who have designed and developed this giant for experimental research work in nuclear transmutations.

Again, at the University of California in Berkeley, Dr. Ernest O. Lawrence and his associates have developed and produced a new type of radiation energy through an electro-magnetic apparatus named the Cyclotron. This generates a potential reaching up to ten million volts, through which is

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